



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/664,468

09/17/2003

Debasis Bagchi

31174/30016A

4351

4743

7590

07/20/2010

MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

EXAMINER

FLOOD, MICHELE C

ART UNIT

PAPER NUMBER

1655

MAIL DATE

DELIVERY MODE

07/20/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/664,468	Applicant(s) BAGCHI, DEBASIS	
	Examiner MICHELE FLOOD	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 June 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 51-70, 76, 84 and 85 is/are pending in the application.
- 4a) Of the above claim(s) 54-70 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 51-53, 76, 84 and 85 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/10/2010</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 10, 2010 has been entered.

Further acknowledgment is made of the receipt and entry of the amendment filed on June 10, 2010 with the cancellation of Claims 71-75, 77-83, 86 and 87; as well as the receipt and entry of the Katz declaration and the declaration filed under 37 § 1.132 of Dr. Debasis Bagchi.

Any rejection or objection present in the previous Office action mail dated January 21, 2010 and not repeated herein is withdrawn.

Claims 51-53, 76, 84 and 85 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 51-53, 76, 84 and 85, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Bomser et al. (U), Moyer et al. (W1), Wedge et al. (V), Dufour et al. (N), Liu et al. (Liu, M et al., J. Agric Food Chem., April 4, 2002, 50: 2926-2930. Antioxidant and antiproliferative activities of raspberries.), Xue et al. (W), Kandil et al. (X) and Gaudout et al. (A*) in view of Prior et al. (U1), Wang et al. (V1), Prior et al. (Prior, RL et al. Journal of AOAC International (2000), 83(4):950-956. Analysis of botanicals and dietary supplements for antioxidant capacity: A review.) and Wang et al. (X1). Newly applied as necessitated by amendment.

Applicant claims a composition comprising constituents of group consisting of blueberry, bilberry, cranberry, elderberry, raspberry and strawberry, wherein the composition is approximately 50% blueberry, 35% strawberry, 7.5% cranberry, 2.5% raspberry, 2.5% elderberry, and 2.5% bilberry based on the total weight of the composition. Applicant further claims the composition in claim 51, wherein the composition has a higher oxygen radical absorbance capacity than an oxygen radical absorbance capacity of any one berry used constituent in the composition; wherein the composition has an oxygen radical absorbance capacity above 40 micromoles of Trolox

Art Unit: 1655

equivalents (TE)/gram fresh weight basis; and, wherein the composition has a higher antioxidant capacity than an antioxidant capacity of any one berry constituent in the composition; wherein the constituents are selected from the group consisting of polyphenols, flavonoids, anthocyanins, or mixtures thereof. Applicant further claims the composition in claim 84, wherein polyphenols comprise ferulic acid, catechin, rutin, and mixtures thereof.

Bomser beneficially teaches, "Fruit extracts of four *Vaccinium* species (lowbush blueberry, bilberry, cranberry, and lingonberry) were screened for anticarcinogenic compounds by a combination of fractionation and in vitro testing of their ability to induce the Phase II xenobiotic detoxification enzyme quinone reductase (QR) and to inhibit the induction of ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine synthesis, by the tumor promoter phorbol 12-myristate 13-acetate (TPA). The crude extracts, anthocyanin and proanthocyanidin fractions were not highly active in QR induction whereas the ethyl acetate extracts were active QR inducers. The concentrations required to double QR activity (designated CD_{qr}) for the ethyl acetate extracts of lowbush blueberry, cranberry, lingonberry, and bilberry were 4.2, 3.7, 1.3, and 1.0 microgram tannic acid equivalents (TAE), respectively, Further fractionation of the bilberry ethyl acetate extract revealed that the majority of inducer potency was contained in a hexane/chloroform subfraction (CD_{qr} = 0.07 microgram TAE). In contrast to their effects on QR, crude extracts of lowbush blueberry, cranberry, and lingonberry were active inhibitors of ODC activity. The concentrations of these crude extracts needed to inhibit ODC activity by 50% (designated IC₅₀) were 8.0, 7.0, and 9.0

Art Unit: 1655

micrograms TAE, respectively. The greatest activity in these extracts appeared to be contained in the polymeric proanthocyanidin fractions of the lowbush blueberry, cranberry, and lingonberry fruits ($IC_{50} = 3.0, 6.0, \text{ and } 5.0$ micrograms TAE, respectively). The anthocyanidin and ethyl acetate extracts of the four *Vaccinium* species were either inactive or relatively weak inhibitors of ODC activity. Thus, components of the hexane/chloroform fraction of bilberry and of the proanthocyanidin fraction of lowbush blueberry, cranberry, and lingonberry exhibit potential anticarcinogenic activity as evaluated by in vitro screening tests.”

Moyer beneficially teaches the total anthocyanins and total phenolic contents and antioxidant capacities as determined by oxygen radical absorbing capacity (ORAC) of fruits of various blueberries (*Vaccinium* L.) in Table 1. Moyer teaches that both blueberry extract and wild blueberry extract have high ORAC values in terms of Trolox equivalents micromoles per gram on fresh weight basis, as well as high contents of anthocyanins and phenolics. Thus, it was known in the art at the time of the invention, that both blueberry extract and wild blueberry extract have high antioxidant capacity as measured by an oxygen radical absorbance capacity assay; and that the highest ORAC values observed in the blueberry (*Vaccinium* L.) population belonged to wild blueberry extract. For example, wild selections of rabbiteye blueberry, *Vaccinium ashei*, from Florida and Georgia had the highest ORAC (131, 129 and 122/ $\mu\text{mol TE/g}$. See Table 1.

In another instance, Wedge beneficially teaches, “Freeze-dried fruits of two strawberry cultivars, Sweet Charlie and Carlsbad, and two blueberry cultivars, Tifblue and Premier were sequentially extracted with hexane, 50% hexane/ethyl acetate, ethyl

Art Unit: 1655

acetate, ethanol, and 70% acetone/water at ambient temperature. Each extract was tested separately for in vitro anticancer activity on cervical and breast cancer cell lines. Ethanol extracts from all four fruits strongly inhibited CaSki and SiHa cervical cancer cell lines and MCF-7 and T47-D breast cancer cell lines. An unfractionated aqueous extract of raspberry and the ethanol extract of Premier blueberry significantly inhibited mutagenesis by both direct-acting and metabolically activated carcinogens.”

Dufour beneficially teaches a composition comprising an anthocyanoside-containing extract derived from the fruit of bilberry, which is used to prevent cancer proliferation in the intestines and colon. Dufour further teaches that the anthocyanosides of the bilberry extract have antioxidant and anti-free radical actions and are not digested in the small intestines but rather assimilated in the terminal part of the colon) and also restores the microbial balance in the intestine by increasing the population of bifidogenic bacteria (resulting in reduction in intestinal pH).

Liu beneficially teaches raspberry extracts rich in anthocyanins and having high antioxidant activity and antiproliferative activity against human cancer cells in a dose-dependent manner. The antioxidant activity of the raspberry was directly related to the total amount of the phenolics and flavonoids found in the raspberry. In Figure 2, Liu illustrates the antioxidant activity of four extracts obtained from four different cultivars of raspberries.

Xue beneficially teaches various fractions of raspberry and strawberry extracts comprising having the ability to inhibit morphological cell transformation in cells treated with B[a]P (benzo[a]pyrene). Extracts comprising ellagic acid, as well as extracts not

Art Unit: 1655

comprising ellagic acid, exerted chemopreventive activity. Xue concludes, "These results suggest that a methanol extract from strawberries and black raspberries may display chemopreventive activity. The possible mechanism by which these methanol fractions (FA-ME, RU-ME) inhibited cell transformation appear to involve interference of uptake, activation, detoxification of B[a]P and/or intervention of DNA binding and DNA repair." Xue further reports that in a study conducted by Stoner et al., freeze-dried strawberry when feed as five or ten percent of the diet, inhibited the development of esophageal cancer.

Kandil beneficially teaches, "Phenolics from the American cranberry (*Vaccinium macrocarpon*) were fractionated into a series of proanthocyanidins and other flavonoid compounds by vacuum chromatography on a hydrophilic, porous polyvinyl gel permeation polymer. Antioxidant activity was not restricted to a particular class of components in the extract but was found in a wide range of the fractions. Significant chemopreventive activity, as indicated by an ornithine decarboxylase assay, was localized in one particular proanthocyanidin-rich fraction from the initial fractionation procedure. Further fractionation of the active anticarcinogenic fraction revealed the following components: seven flavonoids, mainly quercetin, myricetin, the corresponding 3-O-glycosides, (-)-epicatechin, (+)-catechin, and dimers of both gallocatechin and epigallocatechin types, and a series of oligomeric proanthocyanidins." See abstract. Kandil further teaches that the berry fractions have antioxidant capacity.

Finally, Gaudout beneficially teaches that the antioxidant capacity (mmol Trolox® equivalent/ kg of an elderberry extract containing 40% total polyphenols by weight as

Art Unit: 1655

2900-3000, and that the antioxidant capacity (mmol Trolox® equivalent/ kg of a blueberry extract containing 30% total polyphenols by weight as 3500-3600. See Table in Column 8.

The individual teachings of Bomser, Moyer, Wedge, Dufour, Liu, Xue, Kandil and Gaudout, as set forth immediately, teach that it was known in the art at the time of the invention that each of the claim-designated berries of blueberry, bilberry, cranberry, raspberry, strawberry and elderberry was known in the art to contain polyphenols, to exert radical scavenging, anti-oxidative, and anti-cancer activities. None of the references teach a composition comprising constituents of each of the claim-designated berries. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the claim-designated ingredients in the making of the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

The combined references do not specifically teach a composition wherein the composition has a higher antioxidant capacity than that of any one berry constituent in the composition or wherein the composition has a higher oxygen radical absorbance

Art Unit: 1655

capacity than the oxygen radical absorbance capacity of any one berry constituent in the composition, or wherein the composition has an oxygen radical absorbance capacity above 40 Trolox equivalents/gram fresh weight basis. Prior (U1) teaches that the Trolox equivalent antioxidant capacity of blueberry extracts (*Vaccinium* L.), as measured by ORAC, ranged from a low of 13.9 to 45.9 micromole TE/g of fresh berries, depending upon the maturity, the anthocyanin and total phenolic content and variety of the blueberry. See Table 1. Prior further teaches, "Bilberry and the lowbush blueberry blueberries (as taught by Bomser) from Nova Scotia had the highest antioxidant capacity (44.6 +/- 2.3 and 45.9 +/- 2.2, respectively) as well as total phenolics 525 +/- 5.0 and 495 +/- 3.5, respectively) (Table 2). There appear to be clusters of ORAC values in the lowbush blueberries. The first include lowbush-PEI, lowbush-NS, and Fundy lowbush blueberries (Table 2) which were relatively high in ORAC (mean: 41.8), anthocyanins, and total phenolics. The second cluster included lowbush from ME (Table 1), cv. Cumberland, and cv. Blomidon (Table 2) lowbush blueberries which were lower in ORAC (mean: 27.5)." On page 2878, second Column, first paragraph, Prior teaches that the bilberries included in the study represented a mixture of wild clones. Prior further teaches ORAC value of late harvest Tifblue (blueberry rabbiteye cultivar), as taught by Wedge, has a ORAC value of 37.8. See page 2588, Column 2, lines 5-20; Table 1 and Table 2.

Furthermore, Moyer teaches that both blueberry extract and wild blueberry extract have high antioxidant capacity as measured by an oxygen radical absorbance capacity assay; and that the highest ORAC values observed in the blueberry

Art Unit: 1655

(*Vaccinium* L.) population belonged to wild blueberry extract. For example, wild selections of rabbiteye blueberry, *Vaccinium ashei*, from Florida and Georgia had the highest ORAC (131, 129 and 122/ $\mu\text{mol TE/g}$. See Table 1.

Wang teaches that, on the basis of wet weight (edible portion) that strawberry had a relatively high antioxidant capacity of 15.4 $\mu\text{mol Trolox equivalents (TE)/g}$ of fresh weight. In Table I, Wang also (V1) measured the antioxidant capacity of strawberry fruit extract (such as the strawberry extracts taught by Wedge) using the oxygen radical absorbance capacity (ORAC) assay with regard to the effect of acetone extraction time on ORAC (nanomoles of Trolox equivalents per gram) measured in fruit pulp, wherein the TEAC/g ranged from 847 ± 29 (2 min) to 1129 ± 113 (4h). In another instance, Prior (2000) teaches that strawberries, blueberries, cranberries and raspberries have an antioxidant capacity greater than 100, on page 951, last paragraph. Given the teachings as a whole, the artisan of ordinary skill made have had a reasonable expectation that the combining of the ingredients taught by the references as disclosed by Applicant would be a success in providing not only a composition having a higher antioxidant capacity than any one berry extract used in the composition and a higher oxygen radical absorbance capacity than the oxygen radical absorbance capacity than one berry extract used in the composition, but would also be a success in the making of a dietary supplement capable of mitigating the effects of oxidative stress implicated in the pathogenesis of cancer, as well as heart disease. This reasonable expectation of success would have motivated the artisan of ordinary skill to combine the instantly claimed ingredient, especially given the teachings of Prior (For example, on page 2692,

Art Unit: 1655

last paragraph of Column 2, Prior teaches, "Studies are continuing in our laboratory of the implications of consuming foods containing increased quantities of ORAC. The antioxidant rich phytochemicals in strawberries have been shown in rat models to reduce or retard the central nervous system deficits seen in aging [citation omitted] and to protect against the oxidative stress caused by 100% oxygen exposure [citation omitted]. Since the antioxidant capacity of blueberries is higher than for strawberries, a benefit of consuming antioxidants from blueberries would also be expected.

Furthermore, consumption of a more concentrated source of antioxidants will have the greatest impact on in vivo antioxidant capacity. We have estimated that normal intake in humans of antioxidants as measured by ORAC within the U.S. is in the range of 1.2-1.7 mmol ORAC/day [citation omitted]. Increases in serum ORAC are observed with intakes of 3-4 mmol Trolox equiv/day, and some individuals have been observed to have ORAC intakes as high as 6 mmol/day [citation omitted]. Consumption of ½ cup of blueberries (72.5) would increase ORAC intake by 1-3.2 mmol, depending upon the blueberry variety and maturity. Thus, the ORAC of the blueberry source can have marked effects of total daily ORAC intake." Moreover, Gaudout teaches that the antioxidant capacity (mmol Trolox® equivalent/ kg of an elderberry extract containing 40% total polyphenols by weight as 2900-3000, and that the antioxidant capacity (mmol Trolox® equivalent/ kg of a blueberry extract containing 30% total polyphenols by weight as 3500-3600. Furthermore, Wang (X1) suggests that individual anthocyanins (for example, delphinidin, cyanidin, pelargonidin, malvidin and peonidin) found as constituents in each of the claim-designated berries (see Table 1) exert high antioxidant

Art Unit: 1655

potency as measured in ORAC activity and have high Trolox values; and that anthocyanins contribute beneficial health-promoting effects in humans upon administration. Thus, at the time the invention was one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to combine the claim-designated berry constituents taught by the combined references to provide the instantly claimed composition because the claimed invention is no more than the combining of well known ingredients known for their beneficial functional effect to mitigate the effects of free radicals due to their high oxygen radical absorbance capacities and in general beneficial to health and contributing to the proliferation and development of cancer.

The references do not specifically teach using the composition in the amounts claimed by applicant. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been customary for an artisan of ordinary skill to determine the optimal amount of the ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

Art Unit: 1655

Based upon the beneficial teachings of the cited references, the skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Applicant's arguments, as well as the declaration filed under 37 § 1.132 of Dr. Debasis Bagchi, are predicated upon the idea of an unexpected synergistic antioxidant values associated with the instantly claimed composition. While each argument was fully considered, they are not found persuasive in view of the obviousness rejection set forth immediately above. Thereby, Applicant's arguments are considered moot.

With regard to the Katz declaration of Dr. Debasis Bagchi, neither the previous Office action nor the Office action herein has cited the reference coauthored by the invention (the publication Roy et al., Free Radical Research 36(9): 1023-1031.).

Therefore, Dr. Debasis Bagchi are considered moot.

No claims are allowed.

* Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Should you receive inquiries about the use of the Office's PAIR system, applicants may

Art Unit: 1655

be referred to the Electronic Business Center (EBC) at <http://www.uspto.gov/ebc/index.html> or 1-866-217-9197.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE FLOOD whose telephone number is (571)272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele Flood
Primary Examiner
Art Unit 1655

MCF
June 21, 2010

/Michele Flood/
Primary Examiner, Art Unit 1655

Application/Control Number: 10/664,468
Art Unit: 1655

Page 15